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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

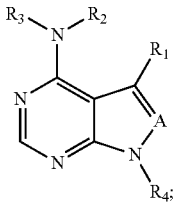
<400> SEQUENCE: 14

Val Met Glu Met Ala Glu Leu Gly Pro Leu Asn
1 5 10

What is claimed is:

1. A pharmaceutical formulation comprising an irreversible, Bruton's tyrosine kinase (Btk) inhibitor having the structure of Formula (A):

Formula (A)



wherein:

A is N;

R_1 is L_2-(substituted or unsubstituted heteroaryl) or L_2-(substituted or unsubstituted aryl), where L_2 is a bond, O, S, —S(=O), —S(=O)$_2$, C(=O), -(substituted or unsubstituted C_1-C_6alkylene), or -(substituted or unsubstituted C_2-C_6-alkenylene);

R_2 and R_3 are independently H or lower alkyl;

R_4 is L_3-X-L_4-G, wherein,

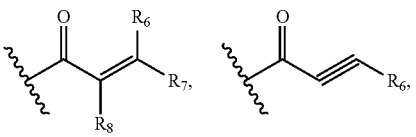
L_3 is optional, and when present is an optionally substituted or unsubstituted alkylene, optionally substituted or unsubstituted cycloalkylene, optionally substituted or unsubstituted alkenylene, or optionally substituted or unsubstituted alkynylene;

X is optional, and when present is O, —C(=O), S, —S(=O), —S(=O)$_2$, —NH, —NR_9, —NHC(O), —C(O)NH, —NR_9C(O), —C(O)NR_9, —S(=O)$_2$NH, —NHS(=O)$_2$, —S(=O)$_2$$NR_9$—, —$NR_9$S(=O)$_2$, —OC(O)NH—, —NHC(O)O—, —OC(O)NR_9—, —NR_9C(O)O—, —CH=NO—, —ON=CH—, —NR_{10}C(O)NR_{10}—, heteroarylene, arylene, —NR_{10}C(=NR_{11})NR_{10}—, —NR_{10}C(=NR_{11})—, —C(=NR_{11})NR_{10}—, —OC(=NR_{11})—, or —C(=NR_{11})O—;

L_4 is optional, and when present is a substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene, or substituted or unsubstituted heterocyclene;

or L_3, X and L_4 taken together form a nitrogen containing heterocyclic ring;

G is



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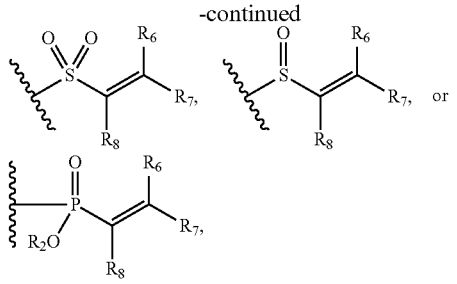


wherein,

R_6, R_7 and R_8 are independently selected from among H, lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl;

R_9 is selected from among H, substituted or unsubstituted lower alkyl, and substituted or unsubstituted lower cycloalkyl;

each R_{10} is independently H, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower cycloalkyl; or

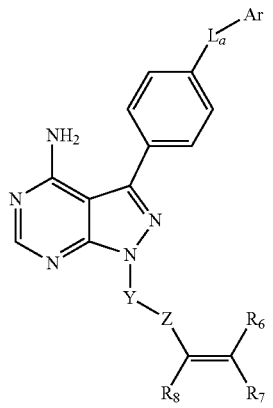
two R_{10} groups can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

R_{10} and R_{11} can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; and

R_{11} is selected from H, —S(=O)$_2$$R_8$, —S(=O)$_2$$NH_2$, —C(O)$R_8$, —CN, —$NO_2$, heteroaryl, or heteroalkyl; or a pharmaceutically acceptable solvate, hydrate, or salt thereof, and a pharmaceutically acceptable excipient.

2. The pharmaceutical formulation of claim **1**, wherein the irreversible, Btk inhibitor is a compound of Formula (D) having the structure:

Formula (D)



wherein:

L_a is O or S;

Ar is phenyl;

Y is a 4-, 5-, 6-, or 7-membered cycloalkylene ring, or

Y is azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl;

Z is C(=O), OC(=O), NHC(=O), S(=O)$_x$, or NHS(=O)$_x$, where x is 2;